IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Steven C. Suffin et al.
Serial No.: 10/697,497 Group No.: 1617
Filed: 10/30/2003 Examiner: Kim, J.M..
Entitled: **Compositions And Methods For Treatment Of Nervous System Disorders**

AMENDED APPEAL BRIEF
APPEAL NO.:

ATTENTION: Board of Patent Appeals and Interferences
Mail Stop - Appeals
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF ELECTRONIC FILING

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Patent and Trademark Office, via EFS.

Dated: March 26, 2009

Traci E. Light

BPAI:

This Amended Brief is in furtherance to the Notice of Appeal mailed by the Applicant on October 17, 2008 regarding the Final Office Action mailed August 7, 2008 and following an Advisory Action/Notification Of Non-Compliant Appeal Brief mailed March 12, 2009. The Notification requests removal of "The Third Declaration By Dr. Steven Suffin" as not timely filed. The Applicants disagree because the data presented within this Declaration is based upon the data previously presented in the First and Second Declarations. Nonetheless, without aquescing to the Examiner's objection the Applicants have removed "The Third Declaration" and argument references thereto, solely for the purpose of proceeding with the Appeal.

This Brief is transmitted as a single copy as per the amended rules. [37 CFR § 41.37(a).]

This Brief contains these items under the following headings and in the order set forth below [37 CFR § 1.192(c)]

I. REAL PARTY IN INTEREST

The real party in interest is Central Nervous System Response, Inc., 2755 Bristol Street, Suite 285, Costa Mesa, CA 92626.

II. RELATED APPEALS AND INTERFERENCES

There are no related applications pending appeal.

III. STATUS OF CLAIMS

Claims 1-3 are rejected and are currently appealed. Claims 4-16 are withdrawn.

IV. STATUS OF AMENDMENTS

All amendments in the case have been entered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The independent claim (Claim 1) recites a formulation (pg 83 ln 7-14) comprising oxcarbazepine (pg 58 ln 13 – pg 59 ln 19) and an antidepressant (pg 43 ln 3-13), wherein the antidepressant comprises bupropion and/or bupropion metabolites (pg 44 ln 25 – pg 47 ln 31). Dependent Claim 2 recites that the formulation further comprises a third drug (pg 3 ln 18-22). Dependent Claim 3 recites the form of the formulation (pg 83 ln 15 – pg 94 ln 27).

VI. GROUNDS OF REJECTION TO BE REVIEWED UPON APPEAL

A. Whether Claims 1-3 are properly rejected under 35 USC § 103(a) as allegedly being unpatentable over United States Patent Application Publication No. 2002/0147196 To Quessy et al. in view of Zakrzewska et al., *J. Neurol. Neurosurg. Psych.*52:472-476 (1989).

B. Whether the Examiner has improperly dismissed rebuttal evidence on the basis of unsupported scientific assumptions.

VII. ARGUMENT

A. The Claims Are Not Obvious

To establish a *prima facie* case of obviousness, three basic elements must be present; i) cited art must contain all the claimed elements; ii) the cited art must provide a reasonable expectation of success for the claimed elements; and iii) some motivation must be present to combine the references and/or secondary evidence. *In re Vaeck,* 947 F.2d 488, 493 (Fed Cir. 1991). In the absence of any one of these basic elements, the basis for obviousness fails.

The Applicants respectfully point out that *KSR v Teleflex* has not changed these basic elements. For example, a *prima facie* case of obviousness still must be constructed by using the standard *Graham* factors: i) the scope and content of the prior art must be evaluated; ii) the level of skill in the art must be determined; iii) differences between the scope and content of the prior art and the claimed embodiment must be identified; and iv) it must be determined whether these identified differences are sufficient to establish obviousness. In addition, the *KSR* decision has determined that both the common sense and general knowledge of one having ordinary skill in the art are considered as part of this legal analysis. The USPTO Guidelines admit as such, and provide for the situations wherein obviousness may be found. The Applicants do not believe that the Examiner has met the burden of these guidelines.

Further, the *KSR* holding only cautioned against a strict application of the "teaching-suggestion-motivation test" such that an explicit teaching is not required to be found within the cited applications. Nevertheless, it is still required to establish a *prima facie* case of obviousness by: i) establishing *some motivation* to combine the references and/or secondary evidence either explicitly or implicitly, ii) establishing that the prior art reference (or references when combined) teach or suggest all the claim limitations; and iii) teaching that the claim could be successfully practiced. The Applicants submit that the Examiner has not made a *prima facie* case of obviousness.

1. Quessy Does Not Support The Examiner's Position

The Examiner has asserted a combination of Quessy et al. and Zakrzewska et al. to support the present obviousness rejection. The Applicants submit that the Examiner has not provided a *prima facie* case of obviousness because the Applicants' claimed embodiment is not predictable from the asserted references.

Contrary to the Examiner's position, Quessy et al. does NOT provide any teaching that oxcarbazepine and lamotrigine have equivalent efficacies. It is the Examiner that is making this assumption. The Examiner, therefore, is offering a completely conclusory argument that is not permitted by long standing patent law.[1] Here, the Examiner is improperly arguing that lamotrigine and oxcarbazepine have the same analgesic activity and efficacy of treating neuropathic pain. This argument has no evidentiary support. The Applicants submit that the Examiner has constructed an improper obviousness rejection.

The Examiner has not provided any scientific data nor pointed to anything within Quessy et al. to support this notion. As such, the Examiner has not fulfilled the burden of creating a *prima facie* case of obviousness, and incorrectly states that:

> It is Applicants' burden to explain any proffered data and establish how any results therein should be taken to be unexpect[ed] and significant relative to the treatment of neuropathic pain.

Final Office Action mailed August 7, 2008., pg 3 ln 13-15. As the Examiner has not fulfilled the burden of showing that oxcarbazepine is (at least) equivalent to lamotrigine it is not the Applicants' burden to show the reverse.

It is clear that the Examiner has not properly considered the scope and content of Quessy et al. Even under *KSR*, this is improper examination procedure.

A showing of evidence is required under *KSR* as the Court reinforced the need for a proper *Graham* analysis to support any obviousness rejection. In one aspect of a proper *Graham* analysis, the Examiner must identify and consider the differences between the

---

[1] The Examiner is reminded that - under the law - an Examiner is NOT one skilled in the art; mere opinion of the Examiner on what one skilled in the art might believe does not count. *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993) ("[T]he examiner's assumptions do not constitute the disclosure of the prior art.").

cited art and the Applicants' claimed invention. In this case, the differences are significant, because unlike the Examiner's argument, Quessy et al. does not teach that lamotrigine and oxcarbazepine are equivalent in treating neuropathic pain, only that they are both sodium channel blockers:

> [0011] Suitable for use as Na^+ channel blockers, referred to herein as Compound(s) (2), are lamotrigine, oxcarbazepine ... It is to be understood that mixtures of these Na+ channel blockers can be employed in the invention if so desired.

Quessy et al., pg 2, lhc. This is the only paragraph within Quessy et al. where "oxcarbazepine" and "lamotrigine' are mentioned together[2]. It is well known in medical science that compounds having similar mechanisms of action have structurally-related differences in efficacy, therefore it is not inherent that two compounds have equivalent effects just because they share a common mechanism of action. To believe otherwise is contrary to the common sense and general knowledge of one having ordinary skill in the art. As lamotrigine and oxcarbazepine are not structurally similar, it would not be expected that they have the same therapeutic efficacy.[3]

This is exactly why *KSR* requires an Examiner to provide an explicit analysis to support an obviousness rejection:

> Often, it will be necessary for a court to look to interrelated teachings of multiple patents ... To facilitate review, this analysis should be made explicit. See *In re Kahn*, 441 F.3d 977, 988 (CA Fed. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness").

KSR v Teleflex, 127 S. Ct. 1727, 1740 (2007) [emphasis added]. This, the Examiner has not done. 'Articulated reasoning" requires a plausible discussion that, at a minimum, compares and contrasts the teachings of an asserted reference with the Applicants'

---

[2] This is also the only place in the Quessy's written description where oxcarbazepine appears.
[3] The Applicants' provided two Declarations by Dr. Suffin showing that lamotrigine and oxcarbazepine have different neurophysiological effects. Additional data is provided below showing similar differences when administered in combination with bupropion.

specification. Merely pointing to single words, without the appropriate context, is wholly insufficient. As shown above, *KSR* cites *In re Kahn* to explain this requirement:

> ... mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole. [*In re Rouffet*, 149 F.3d] *at 1355, 1357.* ... to establish a prima facie case of obviousness ... the Board must articulate the basis ... In practice ... [t]his entails consideration of ... the "scope and content of the prior art" ...

In re Kahn 441 F.3d at 986 [emphasis added]. The Examiner has merely pointed to the term "oxcarbazepine" within Quessy et al. that qualifies only as a 'mere identification in the prior art of each element'. As such, Quessy et al. is not a proper reference to support a *prima facie* case of obviousness and the Examiner is respectfully requested to withdraw the present rejection.

2. Zakrzewska et al. Does Not Fulfill Quessy's Deficiencies

The Examiner introduces Zakrzewska et al. because:

> Zakrzewska et al. teach that oxcarbazepine possesses antineuralgic properties, is effective in the management of intractable trigeminal neuralgia, and elicits an excellent therapeutic response in controlling pain without side effects. It would have been obvious to one of ordinary skill in the art to modify the composition of Quessy et al. by replacing lamotrigine with oxcarbazepine ... [because] ... Zakrzewska et al. also teach that oxcarbazepine has no side effects.

Final Office Action mailed August 7, 2008, pg 6 ln 13 – pg 7 ln 1 [emphasis added], and

> There is a reasonable expectation of successfully treating neuropathic pain without side effects with a combination of bupropion and oxcarbazepine.

Final Office Action mailed August 7, 2008, pg 7 ln 5-7 [emphasis added]. The Applicants submit that Zakrzewska's observation that oxcarbazepine has no apparent side effects does not provide a proper motivation for a combination with Quessy et al. In this regard, the Examiner has overlooked the fact that Quessy et al. teaches that lamotrigine also has no side effects:

> [0038] Lamotrigine (30 $mgkg^{-1}$ b.i.d. p.o.) was dosed chronically for period of 12 days. The dose chosen was determined from previous "in-house" data and doses

> believed to be efficacious in the clinical treatment of neuropathic pain. No adverse side effects were observed as result of the surgery or chronic dosing schedule.

Quessy et al., pg 4, rhc [emphasis added]. Consequently, the Examiner is attempting to create an obviousness argument based upon a problem that does not exist. In other words, Quessy et al. provides no support for the Examiner's argument that one having ordinary skill in the art would be motivated to use Zakrzewska et al. to substitute oxcarbazepine for lamotrigine on the basis of side effects. Zakrzewska et al. provides no such motivation.

Consequently, Zakrzewska et al. fails to form a proper combination with Quessy et al. to support the Examiner's improper obviousness rejection. Specifically, the reference does not teach that lamotrigine and oxcarbazepine have equivalent efficacy nor does the reference show that oxcarbazepine has less side effects than lamotrigine. The Applicants respectfully request that the Examiner withdraw the present rejection.

3. The Applicants Have Provided Data Showing Non-Equivalence Of Lamotrigine And Oxcarbazepine

It is well established law that obviousness may be overcome by showing secondary factors as first established within the *Graham* decision:

> ... *Graham* set forth a broad inquiry and invited courts, where appropriate, to look at any secondary considerations that would prove instructive. *Id., at 17, 86 S. Ct. 684, 15 L. Ed. 2d 545.*

KSR v. Teleflex 127 S. Ct. 1727, 1738 (2007). The legal threshold(s) for obviousness reasserted by *KSR* includes whether or not a combination of known elements have predictable results:

> The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.

KSR v. Teleflex 127 S. Ct. 1727, 1738 (2007). The Examiner bases the present obviousness rejection on the assumption that lamotrigine and oxcarbazepine have equivalent effects. In response, the Applicants have provided two Declarations in past

Office Actions that demonstrate that lamotrigine and oxcarbazepine have opposite neurophysiological effects (i.e., the effects of oxcarbazepine is not predictable based upon the effects of lamotrigine). *See, Section XII Evidence Appendix, Attachments 3 & 4.* Clearly, the Applicants have already shown that oxcarbazepine presents unexpected results.

The First Declaration Of Dr. Suffin showed that lamotrigine and oxcarbazepine have effects on many rEEG multivariables that are opposite and/or have large differences in magnitude and comes to the conclusion that the two drugs are not interchangeable simply because they are both sodium channel blockers.

The Second Declaration Of Dr. Suffin showed opposite effects on rEEG multivariables when comparing a combination of oxcarbazepine/bupropion to a combination of lamotrigine/bupropion. Again, the conclusion from this data is that the two drugs are not interchangeable simply because they are both sodium channel blockers.

In response to both Declarations, the Examiner remained unpersuaded. In regards to the First Declaration, the Examiner states:

> The Suffin Declaration has been carefully review[ed] and considered. However, it is not persuasive because the data showing that oxcarbazepine has an overall rEEG response pattern that is consistent with stimulant drugs which is contrary to lamotrigine having an overall rEEG response pattern that is consistent with depressant changes do not relate to the treatment of neuropathy, rather, the rEEG response pattern relate to characterize features of brain function underlying a broad range of psychiatric syndromes.

Final Office Action mailed August 16, 2007 pg 3 ln 13-19 [emphasis added]. The Examiner's basis on which these Declarations were dismissed is predicated on a general misunderstanding of the Applicants' invention.

4. The Examiner Misunderstands The Applicants' Rebuttal Evidence

The Examiner has provided a response to the Applicants' last response an rebuttal evidence that demonstrates a general lack of understanding regarding the invention:

> Applicants argue that the rEEG data is relevant to neuropathy because that neuro[pathy] is disclosed in the specification as a neurological disorder[]. This is

> not found persuasive because rEEG data is to measure the response pattern related to characterize features of brain function underlying a broad range of psychiatric symptoms. The employment of rEEG data is not a proper indicator to show the effect of neuropathic pain because neuropathic pain involves peripheral nervous system rather than central.

Examiner's Answer, pg 3 [emphasis added]. The Examiner's argument reflects at least two significant misunderstandings (see underlining). First, the Applicants' rEEG data used in rebuttal does not measure response patterns that provide brain features reflecting psychiatric symptoms (i.e., features useful in diagnostics). Rather, the Applicants' rEEG data identifies features that predict an individual's response to a particular drug (i.e., for example, prior to the administration of a drug):

> In one embodiment, this invention relates to predicting the probability of a significant recovery following pharmaceutical treatment of nervous system disorders. In one embodiment, this invention relates to predicting the probability of a significant recovery from a nervous system disorder by a combination of at least two pharmaceutical formulations.

Applicants' Specification, pg 1 ln 5-9 [emphasis added], and

> In one advantage of the present invention, drug responsivity is predicted by a QEEG multivariate Z score. In one embodiment, the individual patient's QEEG multivariate Z scores are compared to a normative population database, wherein an abberant QEEG multivariate Z score is identified. In another embodiment, an individual patient's abberant QEEG multivariable Z score is compared directly with QEEG multivariable Z-scores within the convalescent population database to determine the probability of a significant response to a specific pharmaceutical formulation.

Applicants' Specification, pg 75 ln 28 – pg 80 ln 1[emphasis added]. Second, the Examiner is just plain wrong by stating that neuropathic pain involves only the peripheral nervous system:

> *Phantom Pain*
>
> Damage to somatosensible afferent nerve fibers in the peripheral or central nervous system may often express symptoms involving intractable pain, termed phantom pain (*i.e.,* a form of neuropathic pain). … Weber W. E.,

"Pharmacotherapy For Neuropathic Pain Caused By Injury To The Afferent Nerve Fibers", *Ned Tijdschr Geneeskd.* 145:813-817 (2001).

Central Neuropathic Pain

Central neuropathic pain is a symptom of central nervous system lesions and is difficult to treat. Although it is not necessary to understand the mechanism of an invention, it is believed that neuronal hyperexcitability in damaged areas of the central nervous system plays a major role. The effectiveness of some anticonvulsants (*i.e.*, for example, phenytoin, benzodiazepines, valproate, carbamazepine, pinelamotrigine, gabapentin or topiramate) is believed to be mediated by an increased GABA-mediated inhibition thereby decreasing abnormal neuronal hyperexcitability. These anticonvulsant compounds are considered in the art as effective as the antidepressant amitriptyline. Finnerup *et al.*, "Anticonvulsants In Central Pain" *Expert Opin Pharmacother.* 3:1411-1420 (2002).

Applicants' Specification, pg 65 ln 10 –31. Other references are available in the general medical literature stating that neuropathic pain has both peripheral and central nervous system components. For example, the Examiner is respectfully requested to review the appended Abstracts of: i) Jensen et al., "Management Of Neuropathic Pain", *Curr Opin Support Palliat Care* 1:126-131 (2007); and ii) Tremont-Lukats et al., "Anticonvulsants For Neuropathic Pain Syndrome: Mechanisms Of Action And Place In Therapy" *Drugs* 60:1029-1052 (2000). *See, Section IX Evidence Appendix, Attachments 1 & 2.* Both of these references, in addition to those discussed within the Applicants' specification, teach that neuropathic pain can, and does, involve the central nervous system.

As a result of these general misunderstandings, the Examiner improperly dismissed Applicants' rebuttal evidence showing one drug does not behave the same as the other drug.

In summary, the rEEG multivariables identified by the Applicants' are NOT diagnostic in nature. Rather these multivariables serve as biomarkers that are relevant to the prediction of drug efficacy regardless of an individual's underlying neurological disorder.

In regards to the Second Declaration the Examiner states:

The second Suffin Declaration has been carefully reviewed and considered. However, it is not persuasive because the data showing that oxcarbazepine has an overall rEEG response pattern that is consistent with stimulant drugs which is

> contrary to lamotrigine having an overall rEEG response pattern that is consistent with depressant drugs do not relate to the treatment of neuropathic pain involving peripheral nervous system. Therefore, it is irrelevant to measure the effect of neuropathic pain.

Final Office Action mailed August 7, 2008, pg 4 ln 8-14 [emphasis added]. As argued above, neuropathic pain has central nervous system components as well as peripheral nervous system components. Consequently, the Examiner evaluation and conclusion regarding the data presented within the Second Suffin Declaration requires careful reconsideration. The presented data is highly relevant to the central nervous system components of neuropathic pain.

The Applicants resubmit the First and Second Suffin Declarations for reconsideration that provide relevant data showing that the central nervous system effects of oxcarbazepine (either alone or in combination with bupropion) are unexpected (i.e., for example, opposite) that of lamotrigine, either alone or in combination with bupropion.

Consequently, the Applicants respectfully request the Examiner to withdraw the present rejection.

5. Claims 2 & 3

The Applicants have shown above that Claim 1 is not obvious in view of Quessy et al. and Zakrzewska et al. It is well settled patent law, that nonobviousness of an independent claim is imputed into any and all subsequent dependent claims:

> [D]ependent claims are nonobvious if the independent claims from which they depend are nonobvious.

In re Fritch, 972 F.2d 1260, 1266 (Fed. Cir. 1992). As such, the Examiner is respectfully requested to withdraw the pending rejection.

B. Conclusion

The Appellants submit that the Examiner has not made a *prima facie* case of obviousness. In fact, the Appellants believe that the Examiner has acted in an arbitrary and capricious manner. The Board is reminded that PTO decisions are reviewed using the standard set forth in the Administrative Procedure Act, 5 U.S.C. § 706. *Dickinson v. Zurko*, 527 U.S. 150, 154 (1999). Under that statute, actions are set aside that are arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law. Moreover, factual findings are set aside that are unsupported by substantial evidence. *In re McDaniel*, 293 F.3d 1379, 1382 (Fed. Cir. 2002).

Appellants submit that, with due consideration to all these factors discussed above, the patentability of Claims 1-3 is evident.

For these reasons, the Applicants now appeal because it appears the Examiner has taken an arbitrary and intransigent position. It is submitted that the Examiner's rejections of Claims 1-3 were erroneous, and reversal of these rejections is respectfully requested.

Respectfully submitted,

Dated: March 26, 2009

Thomas C. Howerton
Registration No. 48,650
Attorney for Appellant

Medlen & Carroll, LLP
101 Howard Street, Suite 350
San Francisco, CA 94105
781-828-9870

VIII. CLAIMS APPENDIX

1. A formulation comprising, oxcarbazepine and an antidepressant, wherein said antidepressant is selected from the group consisting of bupropion and bupropion metabolites.

2. The formulation of Claim 1, further comprising a third drug selected from the group consisting of serotonin reuptake inhibitors, monoamine oxidase inhibitors, antipsychotic drugs, antianxiety/anxiolytic drugs, barbituates, stimulants, antiparkinsonian drugs, analgesic drugs, cardiac agents and nutriceuticals.

3. The formulation of Claim 1, wherein the form of said formulation is selected from the group consisting of a tablet, capsule, oral liquid, intrapulmonary liquid, transdermal patch, a polymer-coated tablet, a microparticle, a nanoparticle, an aerosol, fast-dissolve compound and a sterile injectable solution.

IX. EVIDENCE APPPENDIX

Attachment 1:

Jensen et al., "Management Of Neuropathic Pain", *Curr Opin Support Palliat Care* 1:126-131 (2007)(Abstract).

Attachment 2:

Tremont-Lukats et al., "Anticonvulsants For Neuropathic Pain Syndrome: Mechanisms Of Action And Place In Therapy" *Drugs* 60:1029-1052 (2000)(Abstract).

Attachment 3:

First Declaration Of Dr. Steven Suffin

Attachment 4:

Second Declaration Of Dr. Steven Suffin

1: Curr Opin Support Palliat Care. 2007 Aug;1(2):126-31.

Links

Related Articles

Management of neuropathic pain.

Jensen TS, **Finnerup NB**.

Department of Neurology and Danish Pain Research Center, Aarhus University, Aarhus, Denmark. tsjensen@ki.au.dk

PURPOSE OF REVIEW: Neuropathic pain is a chronic pain condition arising from injury or disease of the peripheral or central nervous system with a substantial impact on quality of life. This brief review focuses on the increasing evidence for effective treatments and discusses an evidence-based algorithm for treating neuropathic pain conditions. RECENT FINDINGS: Randomized controlled trials have consistently shown efficacy of tricyclic antidepressants, gabapentin/pregabalin, opioids, tramadol, and serotonin and noradrenaline-reuptake inhibitors for the treatment of various neuropathic pain conditions, lidocaine patches for postherpetic neuralgia and cannabinoids for pain in multiple sclerosis. Carbamazepine or oxcarbazepine is the treatment of choice for trigeminal neuralgia. The efficacy of these drugs in other neuropathic pain conditions as well as the efficacy of lamotrigine and topical capsaicin is questionable, but they may be useful in a subgroup of patients. SUMMARY: For each patient, considerations on the underlying pain mechanisms, immediate and potential long-term side effects, and price as well as comorbidities and concurrent medications will decide which drug should be the first choice, but until further progress is made towards a mechanism-based classification, treatment is likely to be a trial-and-error process where drug combinations may also be considered.

PMID: 18685353 [PubMed - in process]

1: Drugs. 2000 Nov;60(5):1029-52.

Links

Related Articles

Anticonvulsants for neuropathic pain syndromes: mechanisms of action and place in therapy.

Tremont-Lukats IW, **Megeff C**, **Backonja MM**.

Neurology Department, University of Wisconsin, Madison, USA.

Neuropathic pain, a form of chronic pain caused by injury to or disease of the peripheral or central nervous system, is a formidable therapeutic challenge to clinicians because it does not respond well to traditional pain therapies. Our knowledge about the pathogenesis of neuropathic pain has grown significantly over last 2 decades. Basic research with animal and human models of neuropathic pain has shown that a number of pathophysiological and biochemical changes take place in the nervous system as a result of an insult. This property of the nervous system to adapt morphologically and functionally to external stimuli is known as neuroplasticity and plays a crucial role in the onset and maintenance of pain symptoms. Many similarities between the pathophysiological phenomena observed in some epilepsy models and in neuropathic pain models justify the rational for use of anticonvulsant drugs in the symptomatic management of neuropathic pain disorders. Carbamazepine, the first anticonvulsant studied in clinical trials, probably alleviates pain by decreasing conductance in Na+ channels and inhibiting ectopic discharges. Results from clinical trials have been positive in the treatment of trigeminal neuralgia, painful diabetic neuropathy and postherpetic neuralgia. The availability of newer anticonvulsants tested in higher quality clinical trials has marked a new era in the treatment of neuropathic pain. Gabapentin has the most clearly demonstrated analgesic effect for the treatment of neuropathic pain, specifically for treatment of painful diabetic neuropathy and postherpetic neuralgia. Based on the positive results of these studies and its favourable adverse effect profile, gabapentin should be considered the first choice of therapy for neuropathic pain. Evidence for the efficacy of phenytoin as an antinociceptive agent is, at best, weak to modest. Lamotrigine has good potential to modulate and control neuropathic pain, as shown in 2 controlled clinical trials, although another randomised trial showed no effect. There is potential for phenobarbital, clonazepam, valproic acid, topiramate, pregabalin and tiagabine to have antihyperalgesic and antinociceptive activities based on result in animal models of neuropathic pain, but the efficacy of these drugs in the treatment of human neuropathic pain has not yet been fully determined in clinical trials. The role of anticonvulsant drugs in the treatment of neuropathic pain is evolving and has been clearly demonstrated with gabapentin and carbamazepine. Further advances in our understanding of the mechanisms underlying neuropathic pain syndromes and well-designed clinical trials should further the opportunities to establish the role of anticonvulsants in the treatment of neuropathic pain.

PMID: 11129121 [PubMed - indexed for MEDLINE]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Suffin et al.
Serial No.: 10/697,497 Art Unit: 1617
Filed: 10/30/2003 Examiner: Kim, J.
Entitled: **Compositions and Methods for Treatment of Nervous System Disorders**

DECLARATION OF DR. STEVEN SUFFIN UNDER 37 CFR § 1.132

Mail Stop –Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Dated: July 23, 2007 By: Traci L. Eglin

Examiner Joyce:

I, Steven Suffin, M.D. under penalty of perjury, state that:

1. I am one inventor of the embodiments of the invention as claimed in the United States patent application captioned above.

2. I am qualified as an expert in the field of psychiatry and electrophysiological functioning of the brain.

3. I understand that, in the Final Office Action dated January 1, 2007 the Examiner believes that oxcarbazepine can be routinely substituted for lamotrigine because both drugs are classified as sodium channel blockers as suggested in Quessy et al., United States Patent Application Publication No. 2002/0147196.

4. I now provide data showing that lamotrigine and oxcarbazepine do not have similar effects on brain electrophysiology. Chart 6.1 and Chart 6.2 presents normalized Z scores showing the effect of lamotrigine (blue bars) and oxcarbazepine (red bars) on sixty-four (64) rEEG multivariate measurements. Thirty-two (32) of the rEEG multivariate measurements (50%) responded to the two drugs in qualitatively opposite directions. Eleven (11) of the remaining thirty-two (32) rEEG multivariate measurements, while having qualitatively similar responses, differed in magnitude by at least a two-fold difference. Consequently, forty-three (43) of the sixty-four (64) measured rEEG multivariables (i.e., approximately 67%) demonstrated significantly different responses when comparing the effects of lamotrigine to those of oxcarbazepine.

5. Chart 6.1 and 6.2 were assembled by calculating Z scores from response distribution patterns using individual patient data. These differential response patterns between lamotrigine and oxcarbazepine is consistent with our baseline data showing that lamotrigine has rEEG patterns consistent with stimulant drugs while oxcarbazepine has rEEG patterns consistent with depressant drugs. For example, an overall pattern of responses for the rEEG multivariable RPMZPT to several different stimulants are shown in Chart 1, while an overall pattern of responses for the RPMZPT multivariable to several different depressants are shown in Chart 2. Chart 3 (lamotrigine) is easily determined as matching the distribution for stimulants (Chart 1), while Chart 4 (oxcarbazepine) is easily determined as matching the distribution of depressants (Chart 2).

6. The above opposite rEEG effects of lamotrigine and oxcarbazepine were confirmed in trials where pre-drug rEEG measurements were compared to post-drug rEEG measurement in the same individuals (i.e., pair-wise comparisons). Table 1 and Table 2 present data for four (4) different rEEG mulivariates showing opposite effects of lamotrigine and oxcarbazepine.

7. In conclusion, these data show that lamotrigine and oxcarbazepine are not interchangeable simply because they have been suggested to have a mechanism of action in common (i.e., for example, sodium channel inhibition).

Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Dated: July 20, 2007

Stephen Suffin, M.D.

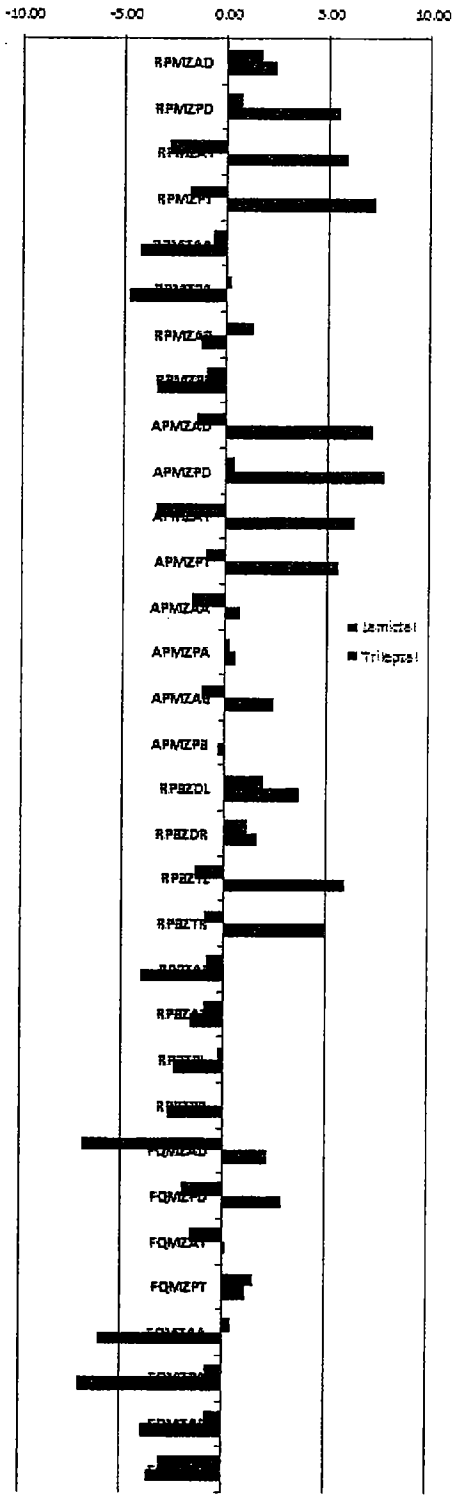


Chart 6.1

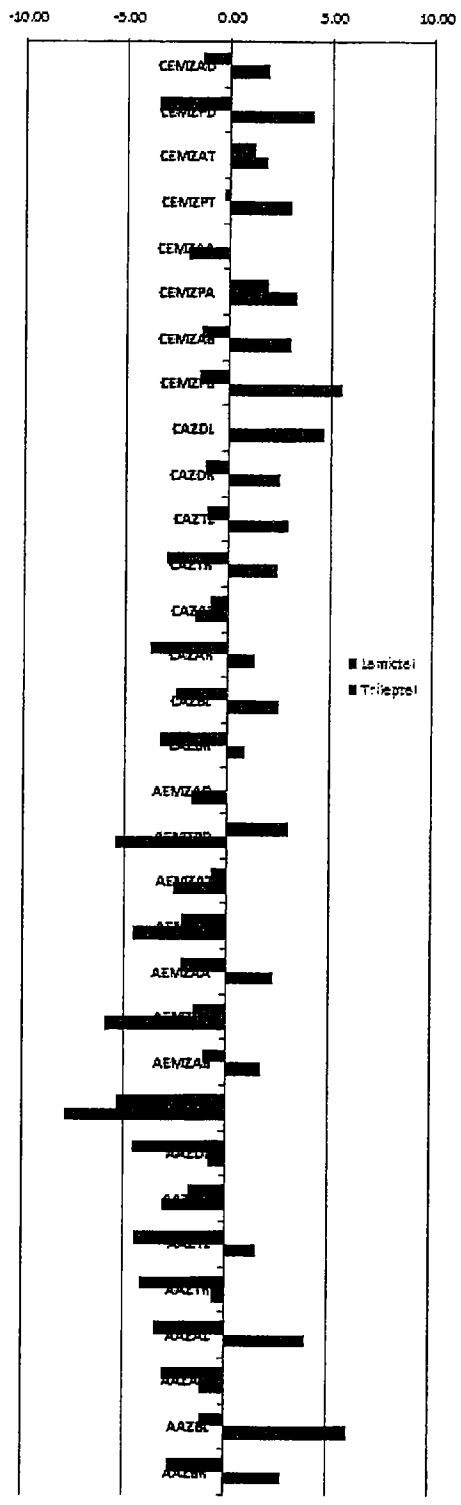


Chart 6.2

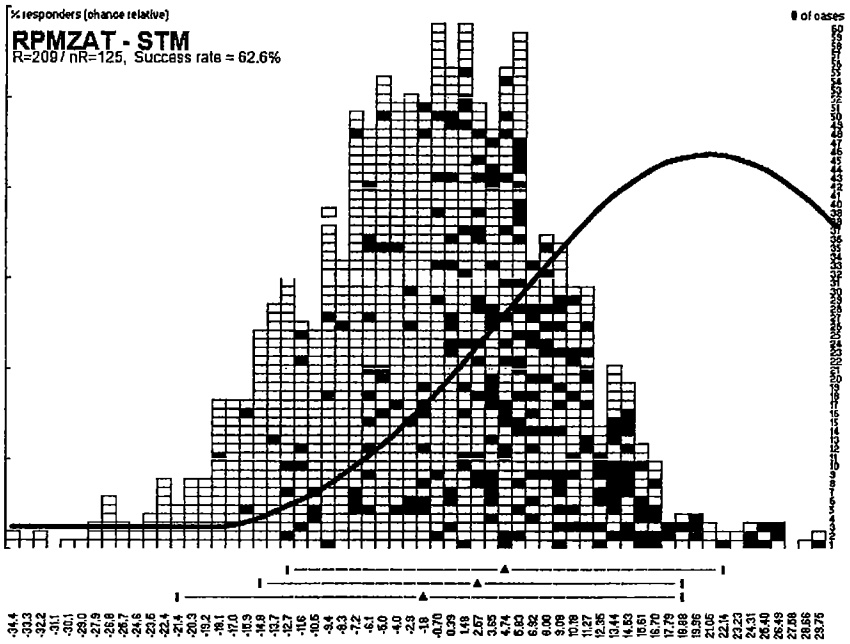


Chart 1

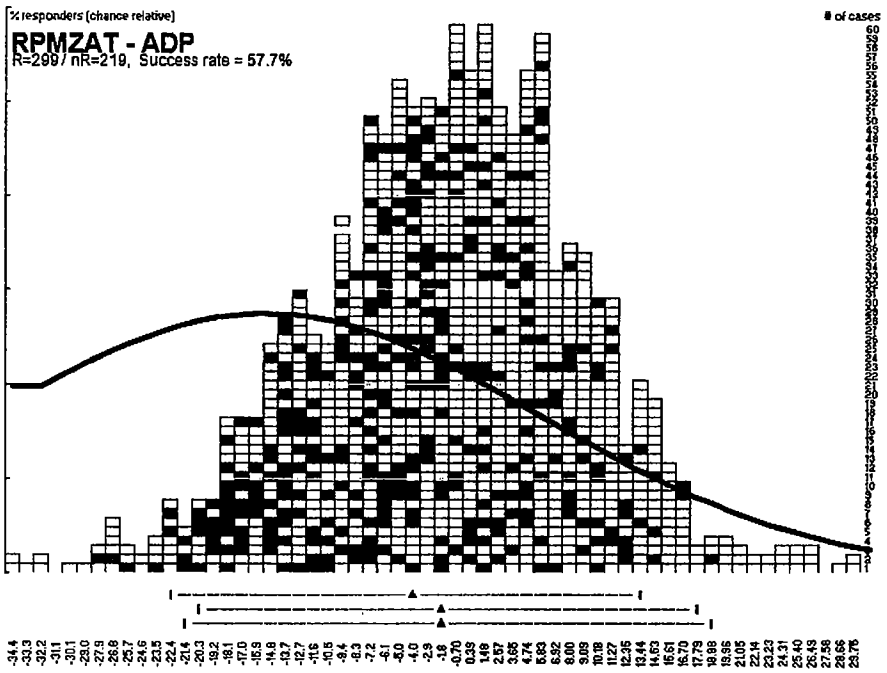


Chart 2

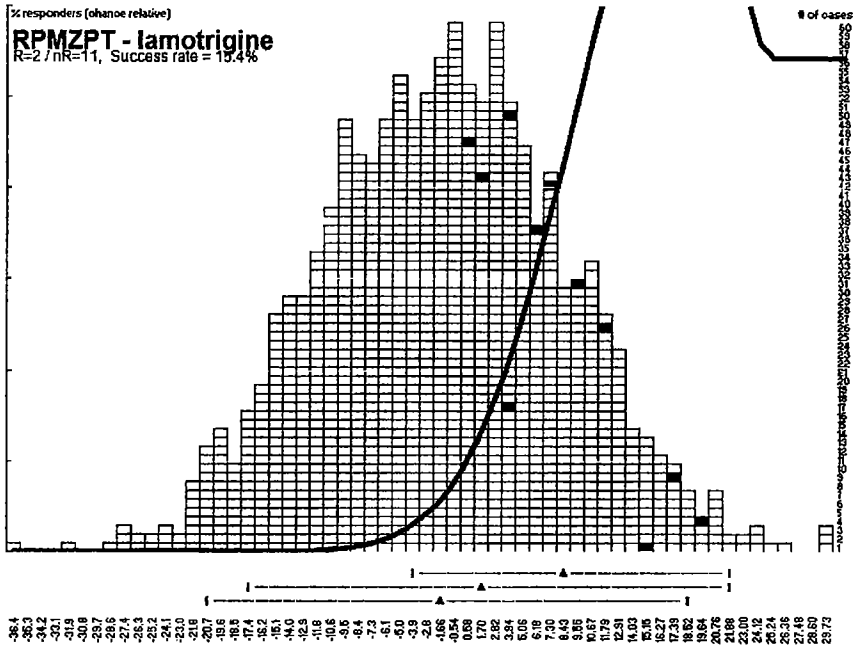


Chart 3

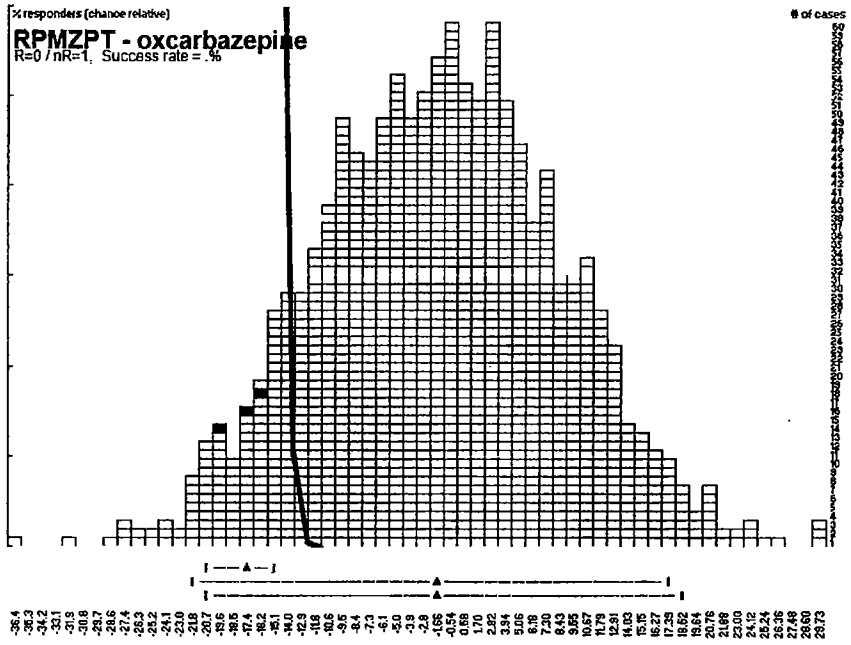


Chart 4

Lamictal

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Average
RPMZAT	-1.1	-11.1	-2.9	-3.2	-1.0	0.2	0.5	-7.0	-3.5	-2.8
RPMZPT	0.8	-2.2	-2.4	-6.7	-0.1	-0.7	5.0	-5.6	-4.1	-1.8
FQMZAA	6.4	-14.1	1.5	0.9	2.3	-1.0	0.7	6.2	1.9	0.5
FQMZPA	2.5	-15.7	0.3	0.1	0.6	-1.3	1.1	-3.8	-2.1	-0.8

Table 1

Oxcarbazepine

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Average
RPMZAT	-4.4	-12.2	5.1	-2.2	2.1	4.3	6.0
RPMZPT	-3.6	-31.3	2.7	-1.4	5.1	2.7	7.3
FQMZAA	0.5	-7.8	-7.2	0.1	-18.3	-3.8	-6.0
FQMZPA	0.3	-16.7	-8.0	-1.1	-14.0	-2.8	-7.0

Table 2

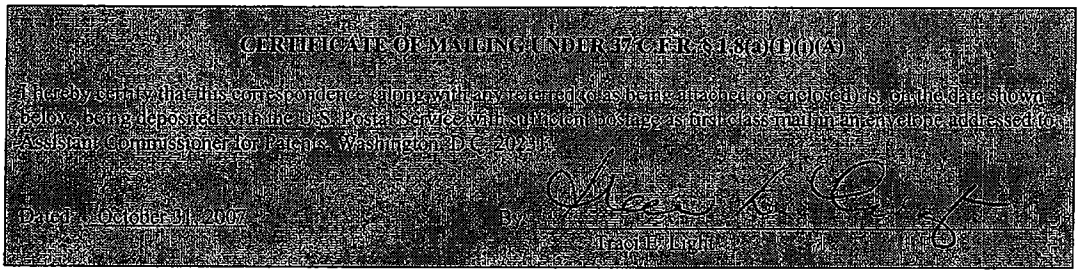
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Suffin et al.

Serial No.:	10/697,497	Art Unit:	1617
Filed:	10/30/2003	Examiner:	Kim, J.
Entitled:	**Compositions and Methods for Treatment of Nervous System Disorders**		

SECOND DECLARATION OF DR. STEPHEN SUFFIN UNDER 37 CFR § 1.132

Mail Stop –Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450



Examiner Joyce:

I, Stephen Suffin, M.D. under penalty of perjury, state that:

1. I am one inventor of the embodiments of the invention as claimed in the United States patent application captioned above.

2. I am qualified as an expert in the field of psychiatry and electrophysiological functioning of the brain.

3. I understand that, in the Final Office Action dated August 16, 2007 the Examiner still believes that oxcarbazepine can be routinely substituted for lamotrigine because both drugs are classified as sodium channel blockers as suggested in Quessy et al., United States Patent Application Publication No. 2002/0147196.

4. The Examiner has apparently not fully understood the impact of the data presented in my first declaration. These rEEG multivariate values were collected after a patient had been given either oxcarbazepine or lamotrigine and demonstrated that the respective effects of these drugs were either opposite and/or quite different in magnitude. The rEEG multivariables listed in the accompanying figures were, in fact, related to treatment effects for neuropathy (unlike the Examiner's stated conclusion).

5. I have also collected rEEG multivariate values for various drug combinations. One drug combination tested was lamotrigine/buproprion and the other drug combination tested was oxcarbazepine/bupropion. Quessy et al. is referred to by the Examiner as suggesting that these two drug combinations would be expected to act in a similar manner just because lamotrigine and oxcarbazepine are both classified sodium channel inhibitors. My data provides evidence that such a conclusion is unwarranted without empirical experimentation.

6. The rEEG multivariate scores for RPMZAT and RPMZPT were raised in value when patients were given oxcarbazepine/bupropion but the rEEG multivariate scores for FQMZAA and FQMZPA were lowered in value.

Welbutrin/Oxcarbazepine										
	Case 1	Case 2	Case 3							Average
RPMZAT	23.9	8.9	0.7							11.2
RPMZPT	24.3	14.7	9.6							16.2
FQMZAA	-6.7	-15.8	-5.2							-9.2
FQMZPA	-8.2	-17.3	-11.0							-12.1

7. The rEEG multivariate scores for RPMZAT and RPMZPT were lowered in value when patients were given lamotrigine/bupropion but the rEEG multivariate scores for FQMZAA and FQMZPA were raised in value.

Welbutrin/Lamictal										
	Case 1	Case 2	Case 3							Average
RPMZAT	-7.1	10.2	5.6							-0.9
RPMZPT	-6.8	2.8	0.7							-1.1
FQMZAA	1.6	6.8	2.3							3.6
FQMZPA	14.1	6.9	2.0							7.8

8. When comparing the above data in Paragraphs 6 and 7, it is clear that drug effects are not always predictable and may not act similarly just because they may have one mechanism of action in common. Many drugs have multiple mechanisms of action, of which some, none, or all may be affected depending on cell and/or tissue type.

9. To believe that all drugs with a similar mechanism of action always are equally effective for all medical conditions is contrary to common clinical practice. Indeed, it is known that giving the same drug to different people for the same diagnosed condition often have opposite effects. For example, the Food & Drug Administration has issued a warning that antidepressants may cause young patients to become more depressed or suicidal:

> Antidepressant Use in Children, Adolescents, and Adults
>
> The U.S. Food and Drug Administration (FDA) today proposed that makers of all antidepressant medications update the existing black box warning on their products' labeling to include warnings about increased risks of suicidal thinking and behavior, known as suicidality, in young adults ages 18 to 24 during initial treatment (generally the first one to two months).

fda.gov/cder/drug/antidepressants/default.htm. My rEEG multivariates allows a clinician to predict how a patient will respond to a drug and/or drug combination before the treatment begins.

10. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Dated: October 31, 2007

Dr. Stephen Suffin

X. RELATED PROCEEDINGS APPENDIX

(No attachments are required for this Brief)